Plasma cell depletion with bortezomib in the treatment of refractory NMDAR-antibody encephalitis. Rational developments in neuroimmunological treatment.

Running title: Bortezomib treatment in NMDAR-antibody encephalitis

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Abstract

Objective: To assess the therapeutic potential of bortezomib in treatment refractory NMDA receptor (NMDAR) antibody encephalitis and its potential in other immune mediated, B-cell driven neurological diseases.

Methods: Two cases of severe NMDAR-antibody encephalitis, resistant to first and second line therapy with steroids, IV immunoglobulins, plasma exchange, cyclophosphamide and rituximab were treated with 4 and 5 cycles of 1.3mg/m2 bortezomib at 350 and 330 days following initial presentation.

Results: Both patients showed significant clinical improvement with reductions of NMDAR-antibody titres following bortezomib treatment. We report the first case in the literature where the NMDAR antibody level was undetectable following treatment with bortezomib.

Conclusion: Bortezomib's unique ability to target long lived autoreactive plasma cells appears to be a useful adjunct to standard second line immunosuppressive therapy in treatment refractory NMDAR-antibody encephalitis. We review the drug's pharmacodynamics, cell targeting and mechanism of action, and postulate that bortezomib may be useful in a host of B-cell driven neuroimmunological diseases.

Introduction

NMDA receptor (NMDAR) antibody encephalitis is the most common antibody mediated autoimmune encephalopathy in the UK.[1] The classical presentation is of evolving prodromal behavioural and personality change, neuropsychiatric features and seizures followed by subcortical features with movement disorders, autonomic dysfunction and reduced consciousness.[2] Around 50% of young females with NMDAR-antibody encephalitis have an ovarian teratoma.[3] A combination of tumour resection and first line immunotherapy (steroids, intravenous immunoglobulin (IVIG), plasma exchange) results in improvement in up to 80% of patients at a median follow up of 24 months.[3] Severe, treatment refractory cases do occur, requiring long term sedation and mechanical ventilation.[4]

The first proteasome inhibitor (PI) used successfully in clinical practice was bortezomib in 2003 for the treatment of multiple myeloma. One small case series and case reports have described clinical improvement using bortezomib in treatment-refractory NMDAR-antibody encephalitis.[5–7]. We report two further cases, one in which the NMDAR antibody level became undetectable following bortezomib treatment, to illustrate the rationale behind proteasome inhibition strategies as novel combination therapy to target B cell driven 'treatment resistant' autoimmune disease.

Both cases provided informed written consent for their clinical information to be published.

Case one

A 35 year old female presented with a rapidly progressive personality disorder, emotional lability and amnesia, followed by headaches and recurrent generalised seizures requiring intubation and sedation. An MRI was performed which was normal. Lumbar puncture revealed cerebrospinal fluid (CSF) protein at 0.58 g/l, with 50 white cells, of which 95% were lymphocytes. NMDAR antibodies in both the serum and CSF were subsequently found to be positive, and therefore 5 days of

intravenous methylprednisolone (IVMP) was given on day 23 following presentation, followed by 5 days of IVIG on day 31 and plasma exchange on day 51.

Pelvic MR imaging on day 25 demonstrated a calcified lesion and surrounding teratoma of the left ovary. On day 47 into admission, a bilateral oophorectomy was performed. Histopathology confirmed bilateral teratomas.

On day 60, the patient was transferred to the National Hospital for Neurology and Neurosurgery (NHNN) neurointensive care unit. An MRI displayed mild hyperintensity of the mesial temporal regions, with volume loss of the right hippocampus. Due to lack of clinical improvement, a more aggressive treatment regime was instigated. The patient received 5 days of plasma exchange on day 65, followed by 3 days of 1g IVMP, then 60mg daily oral prednisolone, before a second round of plasma exchange on day 100. Rituximab 1g was started on day 118, and a second dose 14 days later. The patient was stepped down to the ward 70 days following her admission to NHNN (day 130 from initial presentation) where she remained for a further six months without any signs of clinical improvement. Cyclophosphamide was therefore initiated at 750mg intravenously, with a second dose two weeks following.

At this stage (350 days into the presentation), the patient remained profoundly unwell with neuropsychiatric features of low mood, paranoia, hallucinations and suicidal thoughts. Cognitive assessment demonstrated global impairment of function with a Montreal Cognitive Assessment (MOCA) score of 11/30. NMDAR antibody levels in the serum and CSF remained positive. MR imaging was unchanged. The impression was therefore of ongoing encephalitis. An alternative B cell depletion regimen was therefore started, comprising three cycles of bortezomib 1.3mg/m^2 subcutaneously on days 1, 4, 8 and 11 of a 21 day cycle, in conjunction with oral cyclophosphamide 500mg and dexamethasone 20mg.

Following the third cycle of bortezomib on day 420, the patient began to make significant neurological recovery. Cognitive assessment revealed a seven-point increase in MOCA score to

18/30. The serum NMDAR-antibody titres, persistently positive on 10 previous samples became negative, (see figure 1- undetectable levels at 1:10 dilution). The patient was transferred to the neurorehabilitation unit before discharge home where she is making ongoing improvements in activities of daily living. Her most recent MOCA on day 456 was 21/30, and repeat NMDAR-antibody titre was negative.

Case two

A 49 year old female presented to the Emergency Department following a two week prodrome of headache, myalgia and behavioural changes followed by multiple short lived generalised seizures requiring intubation and transfer to neurocritical care. Rhythmic involuntary movements affecting the face and right upper limb were noted. Infective encephalitis was ruled out, and high levels of NMDAR antibodies in both the CSF and blood were detected (see figure 1).

Extensive investigations of an occult malignancy were performed, all of which were normal. Immunotherapy was started with plasma exchange 5 days into admission, followed by intravenous immunoglobulin at day 20 and intravenous cyclophosphamide day 26. Rituximab was instigated at day 39. Due to lack of improvement, bilateral oophorectomy was performed at day 105. Histology was negative for microscopic teratoma. At this stage, the patient remained bedbound and severely cognitively impaired without signs of improvement. After 11 months the patient was started on bortezomib, and received five subcutaneous doses at 1.3mg/m^2. Over the next four weeks, the patient's rate of recovery improved dramatically. She became more responsive, making purposeful movements and talking. She now lives at home with her husband and is caring for her two young children. She walks unaided with mild balance difficulties and is making continued progress with rehabilitation. Anterograde and retrograde memory continues to improve. Antibody levels have reduced reflecting clinical improvement.

Discussion

Rituximab is now considered a mainstay of treatment for many autoantibody-driven diseases, including anti-NMDAR encephalitis. Rituximab is a monoclonal antibody against CD20, a transmembrane protein expressed exclusively on B cells. Within the B cell lineage, CD20 is expressed on pre-B cells, mature B cells and memory B cells, but its expression is lost during plasma cell differentiation. The presumed mechanism of action of rituximab in autoantibody-driven disease is through indirect depletion of the autoantibody-producing plasma cells as a result of depletion of the pool of pre-B cells and mature B cells. However, long-lived plasma cells, themselves unaffected by Rituximab and persisting after depletion of the B cell precursors, can continue to produce autoantibodies, thereby causing treatment-refractory disease.[8]

Rational therapeutics for autoantibody-mediated diseases would selectively target plasma cells secreting pathogenic autoantibodies. There are no monoclonal antibodies targeting plasma cells currently available, though an anti-CD38 monoclonal antibody (daratumumab) is currently being trialled for treatment of multiple myeloma. Bortezomib primarily inhibits the chymotrypsin-like activity of the proteasome thereby disrupting the ubiquitin-proteasome pathway.[9] This pathway is crucial to target misfolded or damaged proteins for degradation via the endoplasmic reticulum, preventing accumulation and cell apoptosis. Plasma cells secreting large amounts of immunoglobulin are heavily dependent on the proteasome and therefore particularly vulnerable to bortezomib.[10] Following antigenic stimulation, B lymphocytes differentiate into plasma cells. This differentiation is accompanied by a reduction in proteasome activity, and an increased susceptibility to apoptosis in the presence of proteasome inhibitors.[11] Therefore, at least in theory, bortezomib may be an effective targeted therapy in antibody-mediated disease. Indeed, there are a growing number of case reports of its efficacy in refractory autoimmune haematological disorders, [12] ANCA-associated vasculitis,[13] systemic lupus,[14] neuromyelitis optica,[15] as well as NMDAR-antibody encephalitis.

While an attractive adjunct to existing therapies in autoantibody driven disorders, bortezomib has side effects. Although not seen in our patients, one dose-limiting side effect is painful small fibre peripheral neuropathy. As well as inhibiting the proteasome, bortezomib also inhibits serine proteases including HtrA2/Omi, which is thought to protect neurons from apoptosis.[16] Carfilzomib has the same potency for proteasome inhibition, but is longer lasting since it irreversibly inhibits the proteasome and is more selective for chymotrypsin-like subunit of the proteasome.[17] These properties result in fewer off target effects. Promisingly, a phase 3 trial of carfilzomib in multiple myeloma reported peripheral neuropathy in only 1% of patients compared with 6% in those treated with bortezomib.[18]

The optimum treatment regime utilising bortezomib in autoantibody driven disorders remains unstudied, and there are no long-term outcome data to indicate whether patients are at risk of relapse following treatment.

Proteasome inhibitors are showing great promise in the treatment of diseases associated with pathogenic autoantibodies. Within neurology the breadth of antibody-driven diseases has expanded substantially in recent years with the description of antibodies targeting the extracellular epitopes of proteins in the central nervous system. Typically these antibodies cause severe neurological syndromes, which can be very disabling and/or life-threatening, and often respond slowly to standard therapies. Proteasome inhibitors, particularly newer agents with improved side effect profiles, may not only provide a treatment option for cases refractory to standard treatments, but may also be a useful early therapy to rapidly halt the production of pathogenic autoantibodies and thereby lead to earlier neurological improvement.

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